Fermentation and purification strategies for the production of betulinic acid and its lupane-type precursors in Saccharomyces cerevisiae

Microbial production of plant derived, biologically active compounds has the potential to provide economic and ecologic alternatives to existing low productive, plant-based processes. Current production of the pharmacologically active cyclic triterpenoid betulinic acid is realized by extraction from the bark of plane tree or birch. Here, we reengineered the reported betulinic acid pathway into S. cerevisiae and used this novel strain to develop efficient fermentation and product purification methods. Fed-batch cultivations with ethanol excess, using either an ethanol-pulse feed or controlling a constant ethanol concentration in the fermentation medium, significantly enhanced production of betulinic acid and its triterpenoid precursors. The beneficial effect of excess ethanol was further exploited in nitrogen-limited resting cell fermentations, yielding betulinic acid concentrations of 182 mg/L and total triterpenoid concentrations of 854 mg/L, the highest concentrations reported so far. Purification of lupane-type triterpenoids with high selectivity and yield was achieved by solid-liquid extraction without prior cell disruption using polar aprotic solvents such as acetone or ethyl acetate and subsequent precipitation with strong acids. This study highlights the potential of microbial production of plant derived triterpenoids in S. cerevisiae by combining metabolic and process engineering. This article is protected by copyright. All rights reserved.

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